REMARKS/ARGUMENTS

Claims 12, 14, 15, and 17-34 are pending in this application. Claims 1-11, 13 and 16 have been cancelled either previously or in this Amendment. Claims 12, 14, 15, and 17-34 stand rejected. New claim 35 has been added. The issues raised in the final Office Action of July 16, 2010 ("Current Action") are as follows:

* Claims 17-18, and 20 are rejected under 35 U.S.C. § 112, first paragraph, enablement;

* Claims 12, 14, 18-22, 24-27, and 29-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable by the combination of Sweatt and Hall-Jackson;

* Claims 15, 17, and 23 are rejected under 35 U.S.C. § 103(a), as being unpatentable by the combination of Sweatt, Hall-Jackson, and Varga.

Applicant is confused that the Response was not entered but the Examiner responded to the Office Action Response citing new art Roux. If the Examiner intended to add the Roux reference to the 103 rejection then the finality of the Office Action should have been removed because the Applicant has not had a chance to address that art/combination and Applicant had not amended the claims to necessitate the new rejection.

Statement of Joint Inventorship.

Applicants were advised in the prior and in this Office Action of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a). Applicants hereby re-state, as was stated in the last response (Amendment 8/28/09, page 8), that the assignment rights for each inventor were commonly owned by the assignee at the time of each invention as claimed pursuant to 37 C.F.R. § 1.56.

Claims 24 and 26 remain rejected under 35 U.S.C. § 112, first paragraph, enablement.

Applicants respectfully request the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections – Claims 12, 14, 18-22, and 24-27 are rejected under 35 U.S.C. § 103(a)

The Office Action also rejects claims 12, 14, 18-22, and 24-27 as unpatentable under 35 U.S.C. § 103(a) over U.S. Publication No. 2002/0058699 to Sweatt, et al. (hereinafter Sweatt) and Hall-Jackson, et al., in Paradoxical Activation of Raf by a Novel Raf Inhibitor, Chemistry & Biology, August 1999, Vol. 6 pp. 559-568 (hereinafter Hall-Jackson). Applicants respectfully submit that claims 12, 14, 18-22, and 24-27 meet the standard of 35 U.S.C. § 103(a).

Applicant asserts that the combination of Sweatt and Hall-Jackson fails to establish a *prima facie* case of obviousness. Specifically, the combination fails to disclose a method of reducing neuronal cell death in a mammal suffering from or susceptible to neurodegenerative disease, cerebral ischaemia, traumatic neuronal injury, paralysis, or spinal cord injury, comprising administering to the mammal an effective amount of a 3-substituted indolone that is a C-Raf inhibitor or a pharmaceutically acceptable salt-thereof sufficient to reduce neuronal cell death.

Sweatt fails to relate to a neurodegenerative disease; it relates to a Mitogen-Activated Protein Kinase that modulates the activity of potassium channels, which affect neuronal excitability. Sweatt relates to the use of MAPK inhibitors for the treatment of epilepsy and other disorders involving dysfunctional neuronal MAPK activity. As such, Sweatt is not related to a neurodegenerative disease but a protein channel inhibitor for a functioning cell. Epilepsy may be related to nerve tissues but that does not relate to a neurodegenerative disease because epilepsy does not directly cause neuronal loss. The instant specification does state the definition of a neurodegenerative diseases or conditions. Sweatt does not fall into the definition of Neurodegenerative diseases or conditions and cannot teach the instant invention.

> [0024] "Neurodegenerative diseases or conditions" refers to pathological conditions affecting the peripheral nervous system or the central nervous system and characterized by an abnormal loss of neural cells. Such conditions include neurodegenerative diseases including Alzheimer's disease, Parkinson's disease,

> Huntington's disease, Amyotrophic Lateral Sclerosis, cerebral ischaemia, ataxias, epilepsy-associated neuronal loss, traumatic neuronal or spinal cord injury or neurotoxicity, which may be caused by genetic factors or environmental stimuli, or both.

The present invention defines the Neurodegenerative diseases or conditions as an abnormal **loss** of neural cells. Sweatt may disclose an excessive brain neuronal excitability, associated with a seizure disorder but that is not a loss of neural cells. In contrast, the instant specification makes it clear that an abnormal loss of neural cells may be included as a Neurodegenerative diseases or condition only if there is a result of neuronal loss in the explicit restitution of epilepsy-associated neuronal loss in paragraph [0024] above. Sweatt specifically states that, "a seizure represents a discrete, abnormal episode of hyperexcitability in brain structures, influencing motor or sensory function, behavior, or consciousness", (Sweatt [0003]). In contrast, neurodegenerative diseases are a subset of neurological diseases characterized by an abnormal loss of neurons. As demonstrated hereinabove, epilepsy does not cause neuronal loss.

Sweatt states in [0002] that the invention relates to the use of inhibitors of Mitogen-Activated Protein Kinase (MAPK) to modulate the activity of potassium (K+) channels which affect neuronal excitability. This does not state that the cells are dead only defective. The instant invention relates to apoptotic neuronal cell death. In contrast, the instant invention uses a different c-Raf inhibitor to treat a different class of neurological disorders, specifically neurodegenerative disorders, of which epilepsy/seizure is not part of (as found in the teachings of Sweatt). The Examiner agrees with this point in the Advisory Action.

The addition of Hall-Jackson does not cure these deficiencies. The combination still fails to disclose neurodegenerative diseases or conditions as an abnormal loss of neural cells. Hall-Jackson also relates to Mitogen-Activated Protein Kinase that modulates the activity of potassium channels. Again, Hall-Jackson does not disclose the abnormal loss of neural cells. Hall-Jackson concludes, "compounds which inhibit the kinase activity of Raf may not be useful as anticancer drugs" (Hall-Jackson page 559). As a result, the combination of Sweatt and Hall-Jackson cannot disclose neurodegenerative diseases or conditions as an abnormal loss of neural cells since neither Sweatt nor Hall-Jackson teach a neurodegenerative treatment only potassium channel regulation.

In addition, the Applicant has provided support (e.g., Exhibit A and Exhibit B presented in the last response and incorporated herein by reference) on the record that one of skill in the art readily unequivocally understands that epilepsy, "is not considered a neurodegenerative disorder" because epilepsy "is not associated with a chronic deteriorating clinical course or any histopathological evidence or progressive neurodegeneration." Also presented on the records is support for the lack of any connection between epilepsy and neuronal cell death is found in Exhibit C (also presented in the last response and incorporated herein by reference), a printout from the website of the National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) website.

The Advisory Action introduced the Roux reference to support the opinion that epilepsy/seizure are an abnormal loss of neural cells as required by the instant claims. However, Roux fails to provide that link. Roux specifically states in column 2 of page 6887 "Although the **specific contribution of cell death to the pathophysiology of epilepsy remains unclear**, multiple studies suggest that damage produced by status epilepticus (SE) promotes the development of the recurrent spontaneous seizures characteristic of epilepsy (Ait:ardi and Chevrie, 1983; Cavalheiro et al., 1991; Priel et al., 1996)" And "Apoptotic cell death has been reported in some seizure models (Pollard et al., 1994; Morrison et al., 1996; Bengzon et al., 1997), **but the specific contribution of apoptotic or necrotic death to seizure-induced neuronal loss is not clear,** and the cellular mechanisms leading to the induction of apoptosis after seizure are unknown." As such the Roux reference stats the contribution of apoptotic or necrotic death to seizure-induced neuronal loss is not clear. In contrast, Applicants have provided evidence for the lack of any connection between epilepsy and neuronal cell death in Exhibit C (presented in the last response and incorporated herein by reference) and the website of the National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) website.

The combination fails to establish a *prima facie* case of obviousness since the combination fails to provide a suggestion or motivation either in the reference itself, or within the knowledge generally available to one of ordinary skill in the art, to modify the reference; there was a no reasonable expectation of success, and all of the claim limitations were not taught or suggested in the prior art references.

Accordingly, claims 12, 14, 18-22, and 24-27 are not rendered obvious from the combination of Sweatt and Hall-Jackson and/or Roux. Applicant respectfully requests the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

Claims 15, 17 and 23 are rejected under 35 U.S.C. § 103(a)

The Office Action also rejects claims 15, 17, and 23 as unpatentable under 35 U.S.C. § 103(a) over Sweatt and Hall-Jackson in light of Varga. Applicants respectfully submit that claims 12, 14, 18-22, and 24-27 meet the standard of 35 U.S.C. § 103(a).

Applicant asserts that the combination of Sweatt and Hall-Jackson and Varga fails to establish a *prima facie* case of obviousness. For the reasons stated above and incorporated herein by reference the combination of Sweatt and Hall-Jackson fails on all counts to establish a a *prima facie* case of obviousness. The addition of Varga, does not cure these deficiencies. Varga is added to provide a teaching that in cultured cells GW5074 reduces the overactivation of adenyl cyclase in response to treatment with synthetic opioid. As such, the combination of Sweatt and Hall-Jackson and Varga fails to establish a *prima facie* case of obviousness. Applicant respectfully requests the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

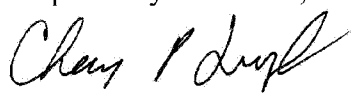
In light of the foregoing, Applicants submit that claims 12, 14, 15, 17-34 and new claim 35 are in condition for allowance, and an early Notice of Allowance of all pending claims is respectfully requested.

In view of the above, Applicant believes the pending Application is in condition for allowance. Applicant believes this paper is being filed with all required fees. However, if any additional fee is due, including those for an extension of time please charge any fees required or credit any overpayment to Chalker Flores, LLP's Deposit Account No. 50-4863 during the pendency of this Application pursuant to 37 CFR 1.16 through 1.21 inclusive, and any other section in Title 37 of the Code of Federal Regulations that may regulate fees. If an extension of time is required with this response but is not included, Applicant hereby petitions for a Request for Extension of Time under 37 CFR 1.136(a).

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: October 18, 2010.

Respectfully submitted,



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